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Original Article

Prognostic Significance of Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio in Diffuse Large B-Cell Lymphoma Patients Treated with R-CHOP

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Objectives : The both values of neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) were reported as indexes of systemic inflammation and readily available and inexpensive prognostic markers in patients with solid cancer. The objective of this study was to clarify whether the NLR and PLR were significant prognostic markers in Korean diffuse large B-cell lymphoma (DLBCL) patients treated with R-CHOP as a first line therapy.

Methods : We retrospectively collected the clinical data of ninety nine DLBCL patients treated with R-CHOP from 2004 to 2012 and analyzed. NLR and PLR were calculated from complete blood count (CBC) and differential leukocyte count.

Results : In univariate analysis, NLR was significantly associated with 5-year progression free survival(PFS) rate (P = 0.039), but not significantly associated with 5-year overal survival (OS) rate (P = 0.276). PLR was not significantly associated with 5-year PFS (P = 0.632) and OS rate (P = 0.855). In multivariate analysis, NLR was not a significant independent prognostic factor for 5-year PFS (P = 0.415) and OS rate (P = 0.991).

Conclusion : The NLR can be considered a useful predictor of survival outcome. The PLR is not a valid predictor of survival outcome.

Key Words: DLBCL, NLR, PLR, Prognostic factor

Recently, as studies on the relationship between cancer and inflammation have increased, interest in the association between the degree of inflammation associated with a tumor and the cancer prognosis has increased.[1,2] Since inflammation provides biomolecular substances such as growth factors in the microenvironment surrounding the tumor, it facilitates proliferation, angiogenesis, invasion and metastasis.[3] In addition, inflammatory cells secrete chemicals known as active oxygen, which induce mutations in nearby cancer cells, thus accelerating the genetic evolution that increases the malignancy.[4] Therefore, the inflammation caused by a tumor is an important indicator of tumor malignancy and general inflammation is an independent prognostic factor related to the survival rate in patients with various cancers.[5] Many biomarkers have been studied as potential tools to measure such general inflammation, but they are too expensive and/or

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difficult to apply in clinical practice due to complicated technical elements. For this reason, studies have been conducted using general inflammation measurement methods that can be performed at low cost and are clinically easy to apply, including CRP (C-reactive protein), Glasgow prognostic score (scoring by measuring CRP and albumin), neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR).[6-9] These methods were studied to determine their prognostic potential in relation to the survival rate associated with various solid tumors such as lung cancer, gastric cancer, pancreatic cancer and colon cancer and were found to be effective in many cases.[10-13]

Neutrophilia is one of the most sensitive indicators of the inflammatory activity of a tumor. It facilitates cell proliferation and tumor metastasis and reduces immune-mediated materials in the host, and is known to cause immune deterioration in the host. Neutrophilia was studied as a prognostic factor for various tumors and has been introduced as an easy and affordable predictive factor.[14,15] Thrombocytosis is caused by the stimulation of megakaryocytes by inflammatory cytokine and the number of platelets in the peripheral blood represents the degree of inflammatory response.[16-18] Therefore, the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and absolute lymphocyte count are well known to reflect the host immunity, were studied in various solid tumors under the expectation that they would display high association with the survival rate and be used as a determination index for clinical prognosis in cancer patients. In most cases, these ratios were confirmed to have high effectiveness.[8,9,19-21] However, those studies were generally related to solid tumors and there are few study results in patients with malignant lymphoma, especially diffuse large B-cell lymphoma (DLBCL).

Many studies show that the absolute lymphocyte count (ALC) is an important predictive factor related to survival rate at the time of diagnosis in patients with diffuse large B-cell lymphoma.[22-24] However, a recent USA study of the neutrophil/lymphocyte ratio at the time of diagnosis was only among patients with diffuse large B-cell lymphoma. In that study, the neutrophil/lymphocyte ratio at the time of diagnosis for a group who received a combination therapy of Rituximab and anti-cancer drug (R-CHOP) treatment, a standard therapy, was reported to be closely related to the progression-free survival rate and overall survival rate and therefore a good prognostic factor.[25] As yet, there are no study results in Korea on the association between the neutrophil/lymphocyte ratio at the time of diagnosis and survival rate in this patient group. Particularly, there are no studies on whether the neutrophil/lymphocyte ratio is significant as a prognostic indicator in B-cell lymphoma yet.

Therefore, this study was to find out the clinical usefulness of the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) as prognostic indicators by investigating if they are

significantly related to the progression free survival rate and overall survival rate in Korean patients with diffuse large B-cell lymphoma who received R-CHOP treatment.

MATERIALS AND METHODS

Patients and Treatment

The subjects of this study were 99 patients who received R-CHOP as an initial treatment for diffuse large B-cell lymphoma that was newly confirmed pathologically in 4 university hospitals located in Pusan and Ulsan from November 2004 to August 2012. R-CHOP treatment is a combination therapy of Rituximab (375 ㎎/㎡, D1), Cyclophosphamide (750 ㎎/㎡, D1), Doxorubicin (50 ㎎/㎡, D1), Vincristin (1.4 ㎎/㎡, D1, up to 2 ㎎), Prednisone (100 ㎎, D1~5) administered in three weeks interval.

Study Method

For study methods, the medical records of participating study institutions were used for retrospective analysis. The subject group was patients with diffuse large B-cell lymphoma identified only by the pathological classification at the time of diagnosis. The basic clinical data, therapies and therapeutic responses of patients were checked and the progress-free survival rate and overall survival were evaluated to find out its usefulness as a prognostic factor. All patients in the selected group had a general blood test (CBC) within 2 weeks before the first treatment and they received R-CHOP treatment for at least 3 cycles. In the event that R-CHOP treatment was discontinued for any reason in less than 3 cycles, the transplant was performed after R-CHOP treatment and the clinical data and test data were insufficient, they were excluded from the study.

Evaluation Method

The neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) were identified through the complete blood count (CBC) and differential leukocyte count tested in peripheral blood. The same classification criteria (3.5) which were published by Porrata et al., in patients with diffuse large B-cell lymphoma was used for the classification criteria of neutrophil/lymphocyte ratio at the time of diagnosis.[25] This criteria was almost consistent with the overall patient average (3.53) examined in this study. Therefore, in this study the progression-free survival rate and overall survival rate were compared in patient groups with a neutrophil/lymphocyte ratio of less than 3.5 at the time of diagnosis and in patient groups with a ratio of more than 3.5. The classification criteria of platelet/lymphocyte ratio was divided into three groups similarly to previous studies.[9,20] In other words, the progression-free survival rate and overall survival rate were compared and analyzed by dividing into three patient groups with a platelet/lymphocyte ratio of less than 150, between 150 and 300 and more than 300 at the time of diagnosis.

In addition, to find out if the platelet/lymphocyte ratio is an independent prognostic factor in diffuse large B-cell lymphoma, other prognostic factors such as IPI (International prognostic index) score, CRP, ferritin, β2-microglobulin, and the presence of bone marrow involvement were examined and analyzed together.

Statistical Method

In this study, the overall survival rate was calculated from the diagnostic date to date of death (regardless of cause) or last follow-up date, and the progression-free survival rate was calculated from the first day of treatment to disease progression or recurrence date. For the survival rate, the Kaplan-Meier survival curve was generated using SPSS version 18.0 and the multivariate analysis was compared and analyzed using Cox regression analysis. It was determined as significant only if the P - value was < 0.05.

RESULTS

Patient Characteristics

The characteristics of subjects are as shown (Table 1). The ages of patients were between 32 and 81 years old and the median age was 60 years old. The ratio of male and female was 53.5 : 46.5, which had almost no difference. The stage of patients registered in this study was evenly distributed as 19%, 28%, 25% and 28% for 1 to 4 stages respectively, according to Ann Arbor staging. Based on ECOG performance status, the status of patients was good in general, accounting for 62% for 0 and 1. The neutrophil/lymphocyte ratio at the time of diagnosis was distributed from 0.05 to 31.85 with a mean of 3.53. The platelet/lymphocyte ratio at the time of diagnosis was varied from 12.61 to 7100.00, with a mean of 302.52.

Analysis on the neutrophil/lymphocyte ratio

The 5-year progression-free survival rate and 5-year overall survival rate obtained from the univariate analysis of patients registered in this study are shown (Table 2). The indicators that had significant differences in progression-free survival rate included IPI score, staging, CRP, β 2-microglobulin, presence of bone marrow involvement and ferritin. Neutrophil/lymphocyte ratios of less than 3.5 and more than 3.5 at the time of diagnosis showed a significant difference (P = 0.039) in 5-year progression free survival rate which were 67.9% and 51.7% respectively. However, the absolute lymphocyte count (ALC) at the time of diagnosis which was shown to be an important prognostic factor in the diffuse large B-cell lymphoma didn't show any significant difference in our data. The indicators that had significant differences in the overall survival included IPI score, LDH (lactate dehydrogenase), staging, CRP, β2-microglobulin and ferritin. But the neutrophil/lymphocyte ratio and absolute lymphocyte count at the time of diagnosis showed no significant difference in the overall survival. The survival curve of the neutrophil/lymphocyte ra-

Table 1. Patient characteristics

Value (%)	N = 99
Age, years	
Median (range)	60 (32 – 81)
Gender (%)	
Male	53 (53.5)
Female	46 (46.5)
IPI (%)	
Low	37 (37.4)
Low-intermediate	28 (28.3)
High-intermediate	13 (13.1)
High	21 (21.2)
LDH	
Normal	39 (39.4)
elevated	60 (60.6)
ECOG (%)	
0 – 1	61 (61.6)
≥ 2	38 (38.4)
Stage (%)	
< III	46 (46.5)
≥ III	53 (53.5)
Extranodal involvement (%)	
< 2	84 (84.8)
≥ 2	15(15.2)
Bulky mass (%)	
< 10 cm	88 (88.9)
≥ 10 cm	11 (11.1)
CRP, mg/dL	
Mean (range)	2.25 (0.01 – 19.15)
β2-microglobulin, mg/L	
Mean (range)	2.45 (0.87 – 9.60)
BM involvement (%)	
Present	16 (16.2)
Absent	83 (83.8)
ALC, x 10^3/mL	
Mean (range)	1770 (40 – 22365)
Ferritin, ng/mL	
Mean (range)	334.76 (7.90 – 4872.40)
Neut/lymph ratio	
Mean (range)	3.53 (0.05 – 31.85)
PLT/lymph ratio	
Mean (range)	302.52 (12.61 – 7100.00)

IPI, international prognostic index; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group (ECOG) performance status; CRP, C-reactive protein; BM, bone marrow; ALC, absolute lymphocyte counts;

Table 2. Prognostic factors for survival in patients with DLBCL by univariate analysis

Value	5yrs PFS (%)	P-value	5yrs OS (%)	P-value
Age, yrs				
< 60	71.6	0.094	70.8	0.231
≥ 60	62.2		66.4	
Gender				
Male	66.8	0.472	63.2	0.265
Female	65.5		72.2	
IPI				
Low/low-intermediate	73.8	0.005*	75.3	0.001*
High-intermediate/high	50.0		51.1	
LDH, (IU/L)				
< 450	74.0	0.119	82.3	0.008*
≥ 450	61.5		56.7	
ECOG (%)				
< 2	70.1	0.322	73.6	0.809
≥ 2	57.5		65.9	
Stage (%)				
< III	82.5	0.014*	85.9	0.007*
≥ III	51.4		50.5	
Extranodal involvement (%)				
< 2	65.3	0.529	67.3	0.926
≥ 2	73.0		65.8	
Bulky mass (%)				
< 10 cm	67.3	0.858	68.4	0.770
≥10 cm	62.3		62.2	
CRP, mg/dL				
< 0.8	81.8	0.005*	82.9	0.001*
≥ 0.8	52.6		55.2	
β2-microglobulin, mg/L				
< 2.5	74.7	< 0.001*	77.8	0.001*
≥ 2.5	36.7		24.1	
BM involvement (%)				
Present	47.7	0.045*	49.7	0.164
Absent	69.8		71.5	
ALC, 1.0 x 10^3/uL				
< 1000	69.4	0.696	81.5	0.390
≥ 1000	67.6		65.0	
Ferritin, ng/ml				
< 500	70.3	0.024*	72.3	0.004*
≥ 500	51.3		46.7	
Neut/lymph ratio				
< 3.50	67.9	0.039*	71.1	0.276
≥ 3.50	51.7		63.0	
PLT/lympho ratio				
< 150	70.8	0.632	67.7	0.855
150~300	67.7		71.4	
≥ 300	60.1		65.0	

IPI, international prognostic index;LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group (ECOG) performance status;CRP, C-reactive protein; BM, bone marrow; ALC, absolute lymphocyte counts

tio at the time of diagnosis (association of progression-free survival rate and overall survival) is presented (Fig. 1).

At the time of diagnosis, the difference in neutrophil/lymphocyte ratio was significant based on univariate analysis of 5-year progression-free survival rate. Additionally, multivariate analysis was performed for progression-free survival rate and overall survival using the IPI score, CRP, β 2-microglobulin and ferritin that were also significant in the survival prediction curve. LDH and staging was significant in univariate analysis but it was excluded since the items were included in the IPI score. The results are presented (Table 3). Through the multivariate analysis, the indicator identified as a factor independent from other factors was β2-microglobulin in the progression-free survival rate and overall survival. According to the multivariate analysis results for the progression-free survival rate on the neutrophil/lymphocyte ratio at the time of diagnosis, the relative risk was 0.619, (95% confidence index was 0.195 - 1.960 and) the significance probability was 0.415. For the analysis results of overall survival, the relative risk was 0.987, (95% confidence index was 0.333 - 2.948 and) the significance probability was 0.991, which has no statistical significance. In addition, the statistical significance of IPI score, CRP and ferritin could not be confirmed in the multivariate analysis.

Analysis of the platelet/lymphocyte ratio

Based on the univariate analysis results that identified the association between progression-free survival rate and overall survival, the platelet/lymphocyte ratio at the time of diagnosis showed 70.8%, 67.7%, and 60.1% of 5-year progression-free survival rate at the ratio of less than 150, between

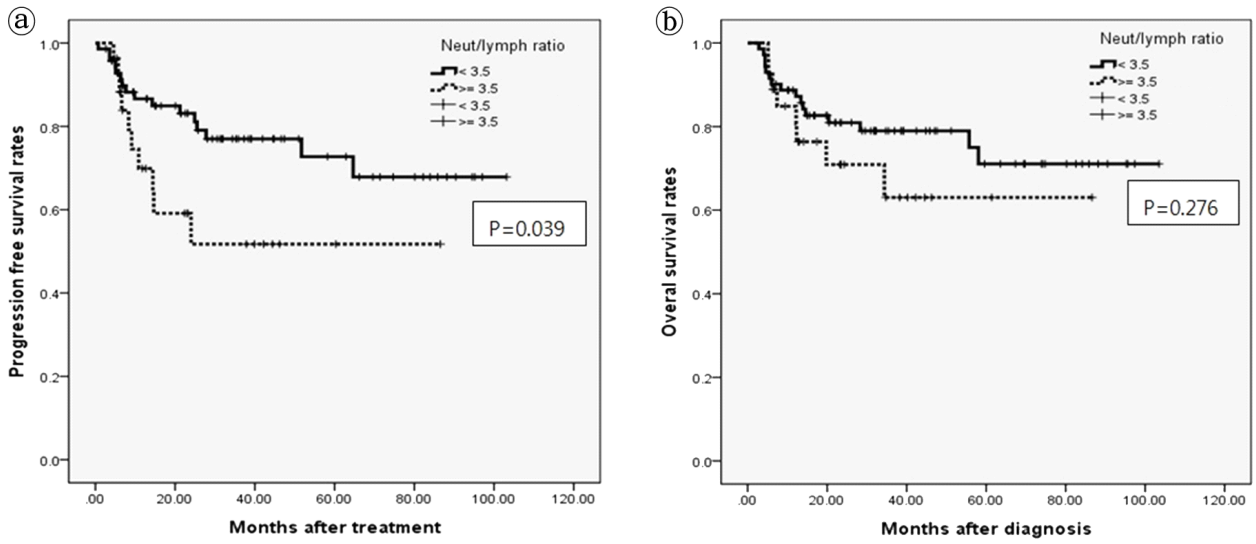

Fig. 1. Five years progression free survival curves and overall survival curves according to Neutrphil/lymphocyte ratio in patients with diffuse large B-cell lymphoma.
a. Five years progression free survival curves
b. Five years overall survival curves

Table 3. Independent prognostic factors for survival in patients with DLBCL by multivariate analysis

Value	PFS			OS		
	RR	95% CI	*p*-value	RR	95% CI	*p*-value
IPI						
Low & low-intermediate						
High-intermediate & high	0.879	0.256-3.013	0.837	0.690	0.211-2.258	0.539
CRP, mg/dL						
< 0.8						
≥ 0.8	1.102	0.283-4.293	0.889	0.591	0.135-2.592	0.485
β2-microglobulin, mg/L						
< 2.5						
≥ 2.5	0. 195	0.064-0.595	0.004*	0.285	0.087-0.936	0.039*
BM involvement (%)						
Present						
Absent	1.637	0.442-6.063	0.461			
Ferritin, ng/mL						
< 500						
≥ 500	0.434	0.118-1.601	0.210	0.458	0.146-1.438	0.181
Neut/lympho ratio						
< 3.50						
≥ 3.50	0.619	0.195-1.960	0.415	0.987	0.333-2.948	0.991

IPI, international prognostic index;CRP, C-reactive protein; BM, bone marrow;

150 and 300 and more than 300, respectively and the overall survival was 67.7%, 71.4%, and 65.0%, showing almost no difference in three groups. At the time of diagnosis, the survival curve of platelet/lymphocyte ratio (association of progression-free survival rate and overall survival) is presented (Fig. 2).

DISCUSSION

In addition to the nature of tumor, the host-response factors are known to be important in determining the clinical prognosis of cancer patients.[26] The items that reflect such host elements include weight loss, performance status and systemic inflammatory response, and these are important indicators for clinical prognosis.[27] Among them, the systemic inflammatory response not only increases the malignancy of the tumor, but also secretes substances such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β) that deteriorate host immunity, causing immunosuppressive effect by weakening the lymphocyte function.[28] In particular, a number of studies measured the function of host immunity with absolute lymphocyte count in malignant lymphoma and found that there was a direct association with the prognosis of the disease. Therefore, the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio at the time of diagnosis of diffuse large B-cell lymphoma, one of the most

common types of malignant lymphomas, were expected to have significant prognosis potential as indicators that better reflect both the tumor-related inflammation and host immunity than the absolute lymphocyte count does.

However, the results examined in this study demonstrated the statistical association between the neutrophil/lymphocyte ratio at the time of diagnosis and progression-free survival rate, but they failed to confirm that it was an independent prognostic factor. In addition, in the overall survival rate, the association was not even demonstrated statistically. Furthermore, the platelet/lymphocyte ratio showed no significant correlation in the progression-free survival rate and overall survival rate. The previously reported study results on the correlation of the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio with the survival rate were mostly investigated in solid tumors, and most of the studies reported that these indicators were related to the survival rate.[8,9,19-21,25] However, these indicators were not identified as independent prognostic factors in all data. Particularly, in three studies that analyzed these two indicators together, there were no results showing both of these indicators were independent prognostic factors.[19-21] In two studies, only the neutrophil/lymphocyte ratio was identified as an independent prognostic factor, and the plateet/lymphocyte ratio was not accepted as an independent prognostic factor.[19,20] In the remaining study, the neutrophil/lymphocyte ratio was not identified as an independent prognostic factor but the platelet/lymphocyte ratio was accepted as an independent prognostic factor.[21] Nevertheless, our

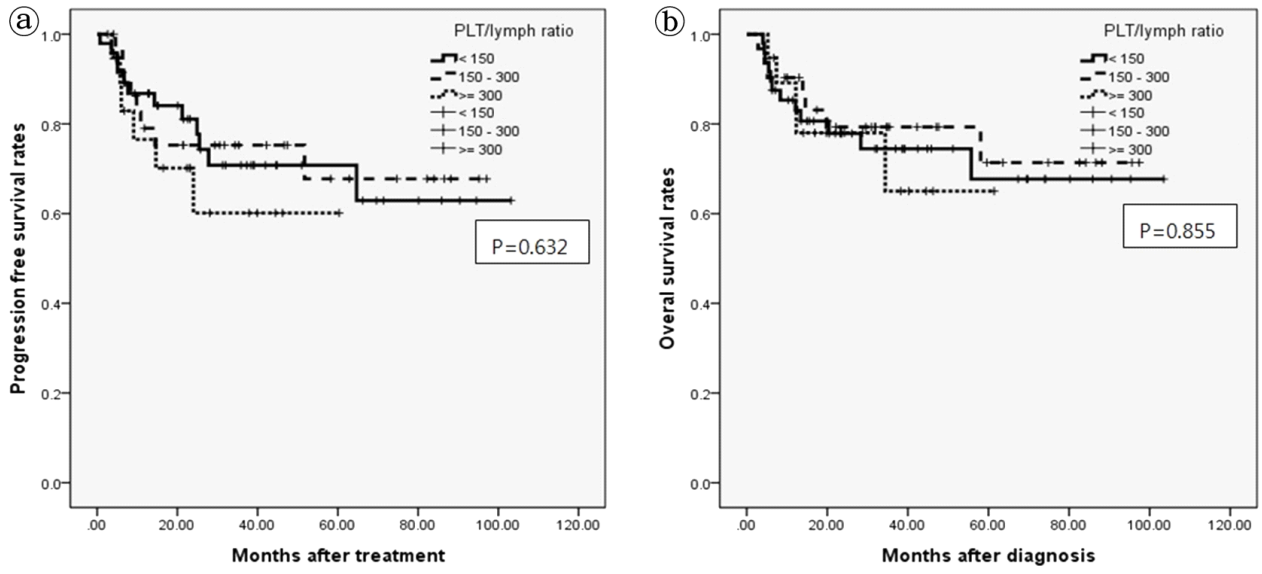

Fig. 2. Five years progression free survival curves and overall survival curves according to Platelet/lymphocyte ratio in patients with diffuse large B-cell lymphoma.
a. Five years progression free survival curves
b. Five years overall survival curves

study results showed that the correlation of the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio and the survival rate was very minor compared to the theoretical background and previous literature. Ultimately, the reasons for this are thought to be the limitations of this study. First, the absolute lymphocyte count that reflects the host immunity had no statistical significance in progression-free survival rate and overall survival rate from the univariate analysis. When referring to previous literature, especially according to the findings in Korean reported by Kim, et al., the absolute lymphocyte count was identified as a significant prognostic factor in patients with diffuse large B-cell lymphoma, while in this study, the significance probability was 0.696 in the progression-free survival rate, which was found to be almost irrelevant. When this was applied to the neutrophil/lymphocyte ratio and platelet/lymphocyte ratio at the time of diagnosis, it had negligible influence on the survival.[22-24] Second, the number of subjects were too small to determine the statistical significance. For the neutrophil/lymphocyte ratio, it is obvious that the survival curve had a tendency to be associated with the survival, but it did not reach statistical significance, and the important reason for this is thought to be the low number of study subjects. Lastly, this study was organized retrospectively and only some of patients were examined during the study instead of examining all patients, so the quality of data may be poor. For this, when analyzing our data, even IPI score which is the most well-known independent prognostic factor in diffuse large B-cell lymphoma had significance only in the univariate analysis and it failed to be identified as an independent prognostic factor in the multivariate analysis.

Although the expected results did not come out in this study, we believe it to be necessary to further study these two indicators as survival prognostic factors in lymphoma, particularly in diffuse large B-cell lymphoma. In particular, based on these study results, the neutrophil/lymphocyte ratio is likely to be considered an easy and inexpensive prognostic factor, whereas it is difficult to determine the effectiveness of the platelet/lymphocyte ratio at this time, and it is prudent to wait and see future study results.

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